

# GENERAL ANÆSTHESIA AND CARDIAC INHIBITION

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The occurrence of cardiac inhibition during general anæsthesia is cited as one of the possible causes of sudden death. The facts concerning the subject are few and it is generally accepted that atropine gives adequate protection. The introduction of the intravenous use of prostigmine as an antidote to curare brings into prominence the question of vagal inhibition during anæsthesia, particularly in view of the recent reports of deaths following the simultaneous intravenous administration of atropine and prostigmine (Macintosh, 1949; Clutton-Brock, 1949).

Reid and Brace (1940) reviewed previous reports about the vagal innervation of the heart and lungs and reported the occurrence of cardiac arrhythmias of ventricular and supraventricular forms following mechanical irritation of the trachea of an anæsthetized patient: they suggested that the irritation caused stimulation of the vagal pulmo-cardiac reflexes with resulting changes in the cardiac rhythm, and advised the use of atropine to prevent the disturbances. Adrian (1933) observed that the stretch receptors in the lungs were unaffected by surgical anæsthesia. Brow, Beattie, and Long (1930) reported that stimulation of the peripheral end of the cut vagus abolished ventricular arrhythmias in anæsthetized animals. In a recent investigation, the author (Johnstone, 1950) observed that the ventricular arrhythmias associated with cyclopropane anæsthesia were the result of sympathetic stimulation due to carbon dioxide accumulation in the body during anæsthesia. The arrhythmias could be abolished either by eliminating the carbon dioxide by assisting the respirations or by increasing the irritancy of the inhaled vapours by adding ether. These observations suggest that the ventricular arrhythmias are of sympathetic origin and can be abolished by vagal stimulation.

The object of the present investigation is to determine to what extent the anæsthetic agent stimulates the pulmo-cardiac reflexes by irritating vagal nerve endings in the air passages. Sixty healthy adults with normal cardiovascular and respiratory systems have been selected, their ages ranging between twenty and fifty years. The operations consisted of herniorrhaphies, colporrhaphies, appendicectomies, hæmorrhoidectomies, and hysterectomies. Anæsthesia was induced in each case with half a gramme of thiopentone and maintained on cyclopropane and ether in a Coxeter-Mushin closed circuit machine. A proportion of them received atropine, as described below. No pre-operative sedatives of any kind were given. A simple oro-pharyngeal airway was used in each case and all patients were in either the supine or lithotomy positions. Only those patients in whom the air passages remained perfectly patent throughout anæsthesia have been included, as obstruction of the passages by spasm or mucus causes increase in the pulse rate. Care was taken to prevent pressure by the face mask on the orbits as this may cause reflex inhibition of the heart.

The galvanometer string of a portable electrocardiograph was under constant observation from before induction till five minutes after the removal of the mask. Tracings were taken at intervals throughout each operation, as described below, and a total of approximately three hundred were developed. All the changes noted below have been confirmed by electrocardiograms. I was personally responsible for the administration of the anæsthetics and the observation of the galvano-

meter string in order to establish the closest possible relation between the clinical details of anaesthesia and the changes in cardiac rhythm. All patients recovered uneventfully.

The investigation has been divided into four sections as follows:

- (1) The effects of cyclopropane-ether anaesthesia on non-atropinized subjects.
- (2) The effects of intravenous atropine during cyclopropane-ether anaesthesia.
- (3) The effects of intravenous atropine during cyclopropane-ether anaesthesia with CO<sub>2</sub> accumulation.
- (4) The effects of atropine pre-medication on cyclopropane-ether anaesthesia.

*Cyclopropane-ether without atropine.* Fifteen patients have been investigated, none of whom received any pre-operative drugs. Anaesthesia was induced with half a gramme of thiopentone and maintained on cyclopropane and oxygen in a closed circuit with CO<sub>2</sub> absorption. Any tendencies towards respiratory depression were overcome by gently assisting the respirations. After twenty minutes of cyclopropane anaesthesia the ether was turned on full for three minutes. The mask was then removed and the lungs ventilated with air. Tracings were taken before induction, immediately after the administration of thiopentone, after twenty minutes of cyclopropane anaesthesia, after three minutes of cyclopropane-ether anaesthesia, and one minute after the removal of the mask.

Sinus rhythm was present in each case prior to induction. The administration of thiopentone caused an increase in the rate in ten patients, a decrease in three, and two were unchanged. Marked slowing of the pulse rate occurred in each case during cyclopropane anaesthesia. The lowest rate was 45 a minute, and A-V nodal rhythm was present in three of them. The addition of ether caused further slowing in eleven, four were unchanged in rate, and A-V nodal rhythm appeared in seven more patients. Sinus rhythm was present and there was a marked increase in the rates within one minute after the removal of the mask in every case (Fig. 1). The greatest increase was from 55 (A-V nodal) to 105 (S-A nodal). There was no evidence of ventricular arrhythmias in any of the patients during anaesthesia.

*Cyclopropane-ether with intravenous atropine.* Bradycardia was induced in fifteen patients by the administration of a mixture of cyclopropane, ether, and oxygen in a closed circuit with CO<sub>2</sub> absorption. No pre-operative drugs were given and sinus rhythm was present in all patients before induction. When bradycardia was established, usually after fifteen minutes of cyclopropane-ether anaesthesia, 1/100th of a grain of atropine, was given intravenously and the anaesthetic continued. Tracings were taken before induction, after fifteen minutes anaesthesia, and half a minute after the injection of atropine.

Complete cardiac arrest occurred in one patient. Sinus bradycardia was present in seven patients and A-V nodal bradycardia in seven during cyclopropane-ether anaesthesia. The administration of atropine was followed, within thirty seconds, by the appearance of sinus tachycardia in each case (Fig. 2). No ventricular arrhythmias were seen in any of the patients with the exception of the case of cardiac arrest that is described below.

*Cyclopropane-ether, CO<sub>2</sub> accumulation, with intravenous atropine.* Cyclopropane, ether and oxygen were administered to fifteen patients, using a closed circuit, without carbon dioxide absorption. None of them received any pre-operative drugs and sinus rhythm was present in all before induction. The occurrence of ventricular arrhythmias during anaesthesia was prevented by increasing the amount of ether in the inspired mixture. After fifteen minutes atropine, 1/100 gr., was injected intravenously and the anaesthetic continued with the absorber turned on. Tracings were taken before induction, after fifteen minutes of cyclopropane-ether anaesthesia, and thirty seconds after the administration of atropine.

The degree of slowing of the pulse during anaesthesia in this series was considerably less than in the previous series in which CO<sub>2</sub> absorption took place. A-V nodal bradycardia occurred in two, increase in the sinus rate in one, and decrease in the sinus rates in the remainder, the lowest rate being sixty beats a minute. Ventricular arrhythmias appeared in each case within thirty seconds after the injection of atropine, multifocal ventricular tachycardia being present in ten and

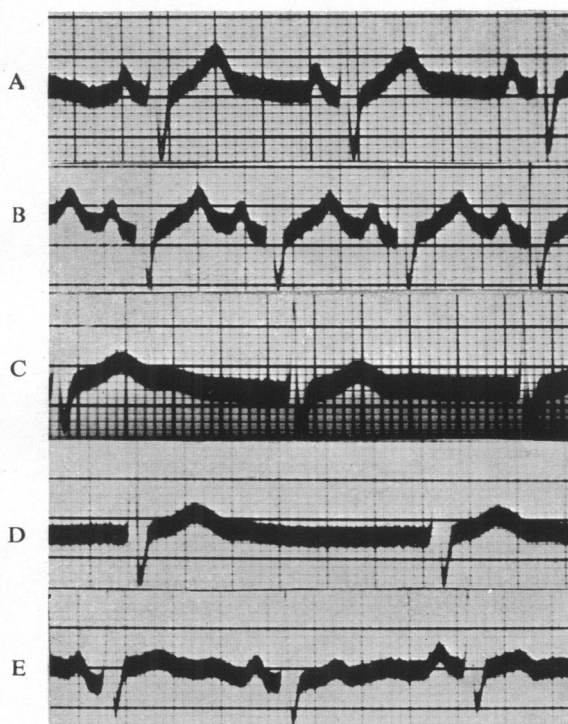


FIG. 1.—Man, 45 years. (A) Before induction. No pre-operative drugs given. (B) Immediately after induction with thiopentone. (C) After twenty-four minutes of cyclopropane anaesthesia with carbon dioxide absorption. (D) Ether added to the circuit three minutes previously. (E) Mask removed one minute previously.

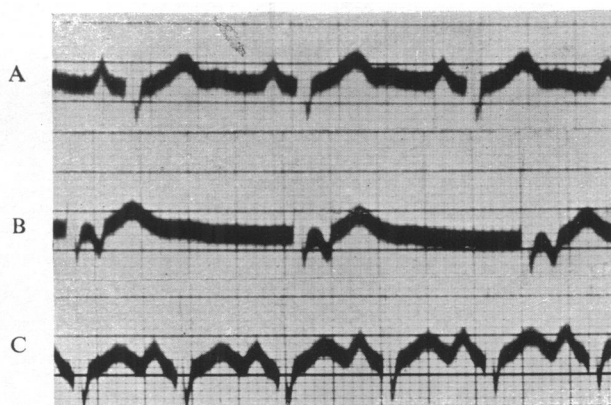


FIG. 2.—Man, 23 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anaesthesia with carbon dioxide absorption. (C) Atropine, gr. 1/100, administered intravenously thirty seconds previously.

bigeminal rhythms in five. The bigeminal rhythms consisted of alternating sinus beats and ventricular extrasystoles, the pulse rate being rapid. The insertion of the  $\text{CO}_2$  absorber caused the disappearance of the ventricular arrhythmias within four or five minutes in each case, with the appearance of sinus tachycardias of between one hundred and thirty and one hundred and fifty beats a minute (Fig. 3 and 4).

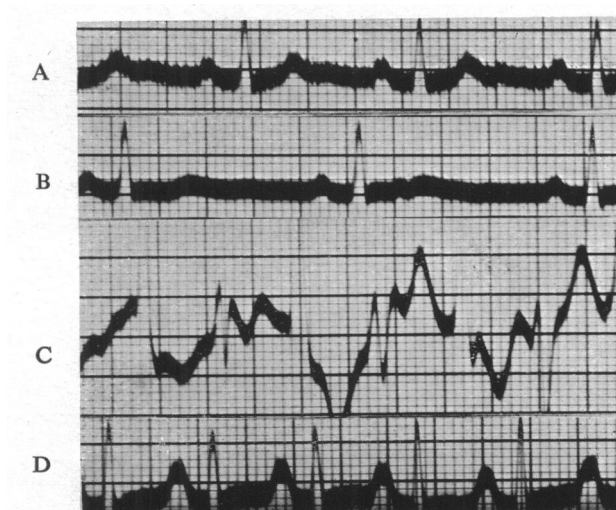


FIG. 3.—Man, 34 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anaesthesia with carbon dioxide accumulation. (C) Atropine, gr. 1/100, administered intravenously thirty seconds previously. (D) Carbon dioxide absorber inserted into circuit three minutes previously.

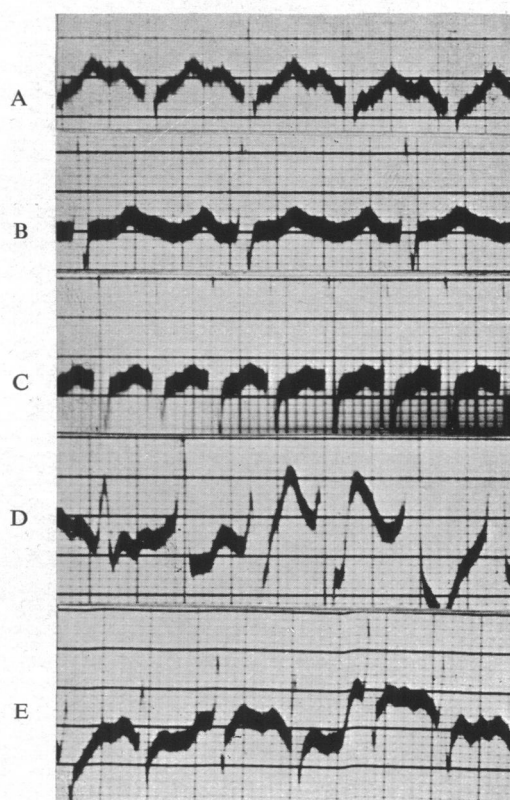


FIG. 4.—Man, 28 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anaesthesia with carbon dioxide accumulation. (C) Atropine, gr. 1/100, administered intravenously fifteen seconds previously. (D) Atropine thirty seconds previously. (E) Carbon dioxide absorber inserted three minutes previously.

*Atropine pre-medication with cyclopropane-ether.* Fifteen patients undergoing operations for appendicitis, hernia, or hysterectomy received atropine, gr. 1/50, by intramuscular injection twenty minutes before the induction of anæsthesia; sinus rhythm was present in all of them. Anæsthesia was induced with half a gramme of thiopentone in each case and maintained on cyclopropane and oxygen in a closed circuit with CO<sub>2</sub> absorption. Any tendencies towards respiratory depression were overcome by gently assisting the respiration. After twenty minutes of cyclopropane anæsthesia ether was added for a period of three minutes. The mask was then removed and the lungs ventilated with air. Tracings were taken before induction, after induction with thiopentone, after twenty minutes of cyclopropane anæsthesia, after three minutes of cyclopropane-ether anæsthesia and one minute after the removal of the mask.

The administration of thiopentone was followed by an increase in the sinus rate in four patients, a decrease in two, and nine were unchanged. During cyclopropane anæsthesia tachycardia was present in every case, being of sinus origin in thirteen and of A-V nodal origin in two. The addition of ether caused no marked change in the pulse rates but caused pacemaker shift to the A-V node in five more patients. One minute after the removal of the mask sinus tachycardia was present in every case (Fig. 5). No ventricular arrhythmias were observed.

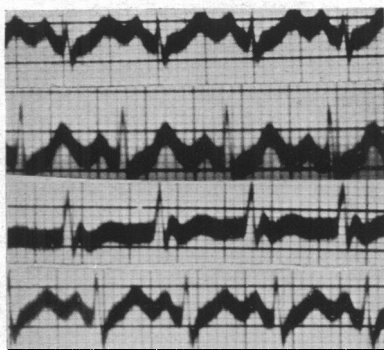


FIG. 5.—Woman, 45 years. (A) Before induction. Atropine, gr. 1/50, given intramuscularly twenty minutes previously. (B) After twenty minutes of cyclopropane anæsthesia with carbon dioxide absorption. (C) Ether added three minutes previously. (D) Mask removed one minute previously.

#### CARDIAC ARREST DURING ANÆSTHESIA

Cardiac arrest has been encountered in two patients. One occurred in the present investigation and one in a previous work (Johnstone, 1948). Details of these cases are as follows.

Case 1. M.R., 36 years. A healthy, well-nourished woman undergoing dilatation of the cervix and curettage of the uterus for an incomplete abortion. No anæmia. No pre-operative drugs given. Anæsthesia was induced with half a gramme of thiopentone and maintained on cyclopropane and oxygen in a closed circuit with carbon dioxide absorption. After fifteen minutes of cyclopropane anæsthesia the ether was turned on for one minute and the mask was then removed.

The pulse became progressively slower from the start of the inhalation anæsthetic and, after sixteen minutes of cyclopropane-ether anæsthesia, complete cardiac arrest occurred and lasted for approximately forty-five seconds. Atropine, gr. 1/100 was injected intravenously a few seconds before the onset of complete arrest. The anæsthetic was then removed and the lungs were flushed out with air by manual pressure on the re-breathing bag. The pulse returned in about thirty seconds and the patient recovered uneventfully. Details of the electrocardiography are shown in Fig. 6. It will be seen that the period of cardiac arrest was followed by a period of ventricular tachycardia. Unfortunately the patient was returned to the ward before this arrhythmia had subsided as her general condition was satisfactory. A tracing taken one hour after the operation showed a normal sinus rhythm at ninety-five beats a minute. At this time the patient was fully recovered.

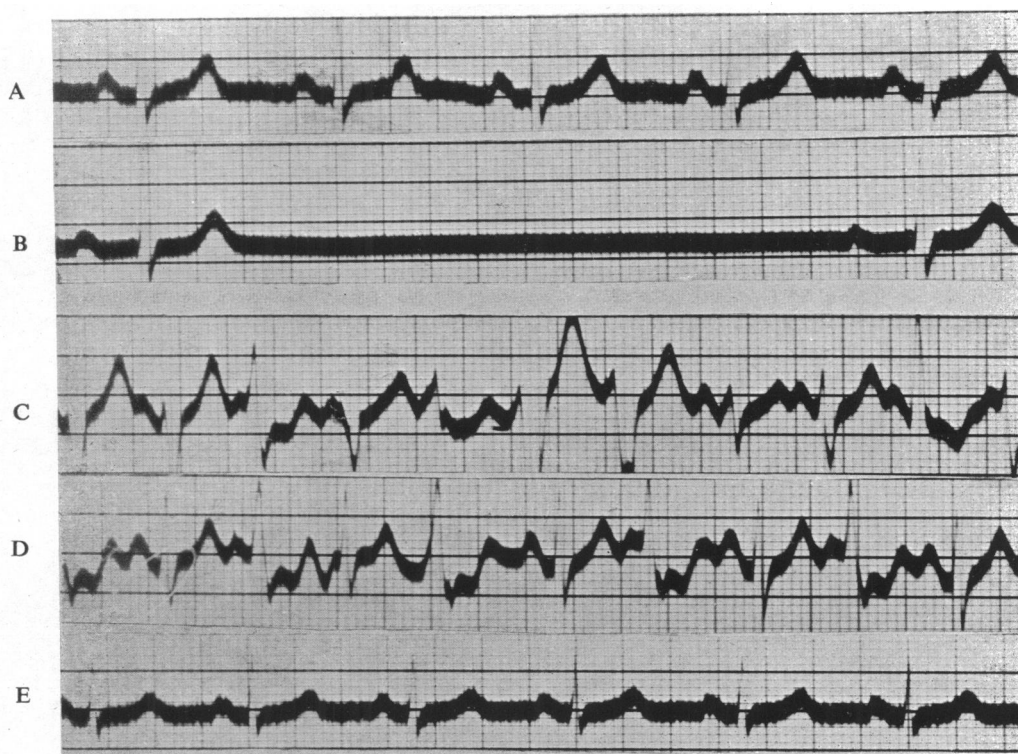


FIG. 6.—Woman, 36 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anaesthesia with carbon dioxide absorption. Approximately forty-five seconds of complete cardiac arrest followed the taking of this tracing. (C) One minute after the removal of the mask and the intravenous administration of atropine gr. 1/100. (D) Two minutes after the removal of the mask. (E) One hour after the operation.

Case 2. J.G., 41 years. A healthy, muscular man undergoing herniorrhaphy. No pre-operative drugs given. Anaesthesia was induced with half a gramme of thiopentone and maintained on trichlorethylene, nitrous oxide and oxygen with a Boyle's apparatus. After sixteen minutes of trichlorethylene anaesthesia, the ether was turned on and continued for six minutes. The mask was then removed and anaesthesia discontinued. Details of the electrocardiography are shown in Fig. 7.

During the period of trichlorethylene anaesthesia the sinus rate gradually dropped from one hundred and thirty beats a minute to fifty beats a minute. After the addition of ether for five minutes, complete A-V block occurred with ventricular standstill which lasted for approximately forty-five seconds. The mask was then removed and ventricular contractions re-commenced in thirty seconds. A sinus rate of sixty beats a minute was present three minutes after the removal of the mask. During the period of ventricular standstill the auricles were contracting at forty-five beats a minute and spontaneous respiration was present. The patient made an uneventful recovery.

#### DISCUSSION

These observations indicate that vagal inhibition of the heart occurs during the inhalation of an anaesthetic, the degree of inhibition varying directly with the irritancy of the inhaled vapour. It is probable that the anaesthetic stimulates sensory nerve endings in the lungs with resulting cardiac inhibition through the pulmo-cardiac reflexes. If the inhibition were due to a more central effect of the anaesthetic there would not be such a prompt reversal of the changes after the removal of the

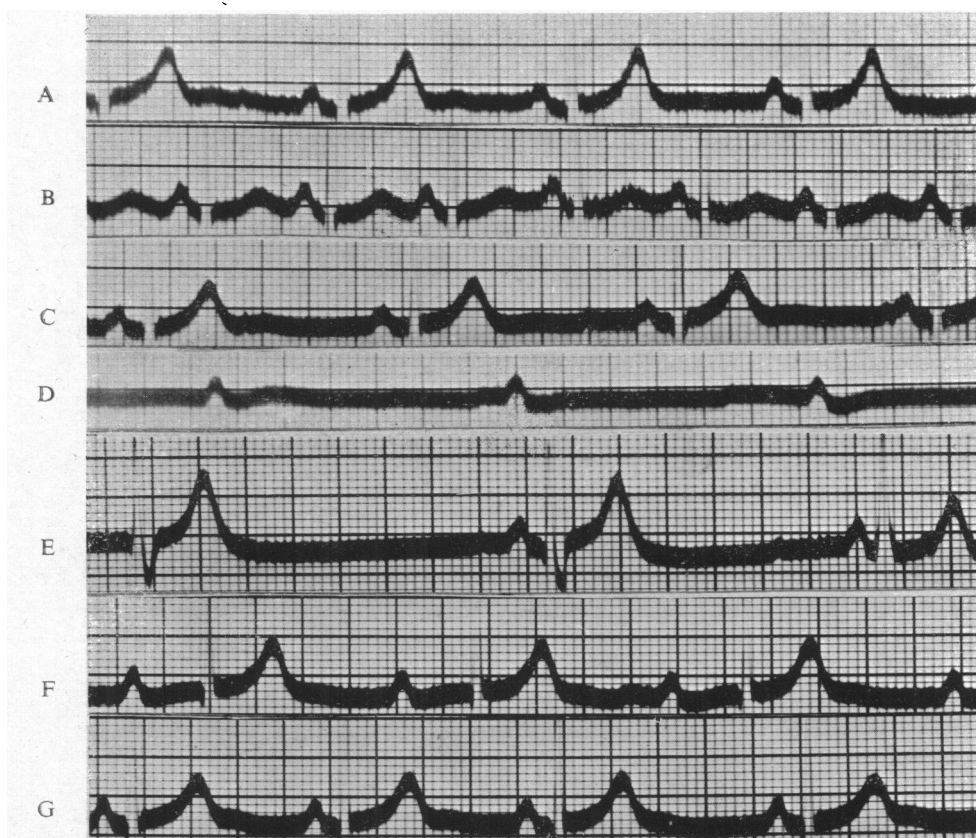


FIG. 7.—Man, 41 years. (A) Before induction. No pre-operative drugs given. (B) Immediately after induction with thiopentone. (C) After ten minutes of trichlorethylene anaesthesia. (D) Ether added six minutes previously. (E) Mask removed half a minute previously. (F) Mask removed one minute previously. (G) Mask removed three minutes previously.

face mask. The arrhythmias to which the inhibition gives rise include sinus bradycardia, A-V nodal rhythm, partial and complete A-V block, ventricular standstill, and complete cardiac arrest.

The pre-operative administration of atropine prevents the more dangerous degrees of inhibition, such as S-A nodal or A-V nodal bradycardia, A-V block, and cardiac arrest. Wilson (1915) pointed out that atropine had a more selective action on the A-V node in protecting it from the effects of vagal stimulation. He demonstrated the occurrence of A-V nodal escape during orbital pressure in atropinized subjects and suggested that the escape occurred because the "period" of the S-A node was depressed below the "period" of the A-V node with the result that the latter node became the pacemaker. My observations indicate that a similar reaction occurs during anaesthesia. Best and Taylor (1927) have stated that  $\frac{1}{20}$ — $\frac{1}{15}$  of a grain of atropine, is required to annul completely the effects of vagal stimulation in man. This probably accounts for the high incidence of A-V nodal rhythm during anaesthesia when smaller doses of atropine are given pre-operatively.

The pre-operative administration of atropine in doses up to, gr. 1/50, protects most patients from serious cardiac inhibition during anaesthesia. I have, however, observed bradycardia and partial A-V block during the induction of anaesthesia with ether in a jaundiced patient who had received atropine, gr. 1/50, pre-operatively. Sprague (1929) has reported the progressive slowing of the pulse to complete cessation and death of a jaundiced patient induced with ether. It is important, therefore, to watch carefully for the patient with increased vagal tone, e.g. patients with jaundice, simple sinus bradycardia or peptic ulceration. High concentrations of anaesthetic vapours should

be avoided in such patients. Judging from preliminary observations, it is probable that atropine, gr. 1/100 intravenously gives protection for approximately thirty minutes and atropine, gr. 1/50 intramuscularly for ninety minutes after administration.

In addition to releasing the S-A and A-V nodes from the effects of vagal inhibition during anaesthesia, the intravenous administration of atropine to anaesthetized subjects may release the ventricular centres and give rise to the serious complication of ventricular tachycardia. This complication is particularly liable to occur in patients in whom carbon dioxide has been allowed to accumulate during anaesthesia. Auricular tachycardia sometimes precedes the onset of ventricular tachycardia by a few seconds but I was unable to verify this point fully as the facilities for continuous photography were not available. I obtained a tracing in one patient (Fig. 4C). In this investigation the rise in carbon dioxide tension was deliberately induced by excluding the absorber from the circuit. A similar rise may occur after prolonged deep anaesthesia, particularly in curarized patients, when respiration has been depressed and no effort made to assist the respiratory exchange by rhythmic manual compression of the re-breathing bag.

Dameshek *et al.* (1938) have observed the occurrence of sinus and ventricular tachycardias in some patients after subcutaneous administration of acetyl-B-methylcholin chloride. They suggested that this action was probably due to stimulation of the cholinergic sympathetic ganglia. It may be assumed that the intravenous use of prostigmine may sometimes have a similar action. Thus, the simultaneous intravenous administration of atropine and prostigmine to anaesthetized subjects may release a sympathetic stimulation of sufficient intensity as to precipitate a fatal ventricular fibrillation. This may have been the mechanism of the sudden deaths to which I referred at the beginning of this paper. On the other hand, the cardiac failure may have been caused by vagal inhibition due to the action of prostigmine, as atropine, gr. 1/100, would not give complete protection from a sudden para-sympathetic stimulation.

The important point established by this work is that the simultaneous intravenous administration of atropine and prostigmine to anaesthetized patients is a dangerous procedure. The only way in which this danger can be overcome is to give minimal doses of curare and thereby eliminate the need for prostigmine. There is no doubt that the judicious use of curare is of considerable benefit to anaesthesia as it reduces the amount of anaesthetic required, particularly in abdominal surgery. The use of this drug does not eliminate the necessity for moderately deep anaesthesia in order to inactivate the laryngeal reflexes. Wright (1940) stated that the drug has no effect on the vagus. Laryngeal or bronchial spasm may therefore occur in lightly anaesthetized patients. The effect of curare on these spasms is merely to mask the straining which ordinarily occurs in the respiratory musculature.

I have used curare extensively for abdominal surgery and in no case has it been found necessary to administer a second dose after the initial 15 mg. The curare is given intravenously as soon as the patient is in the first plane of surgical anaesthesia and the laryngeal reflexes have been abolished. The relaxation which this amount of curare produces can be maintained indefinitely with cyclopropane and a trace of ether. It is perfectly safe and easily reversible. This procedure eliminates the need for prostigmine in so far as abdominal surgery is concerned. Adequate oxygenation must be maintained by manually assisting the respiration. Mautner and Luisada (1941) have observed that oxygen lack tends to neutralize the effect of curare on voluntary muscle in animals.

It will be noted that A-V nodal rhythm occurs frequently during anaesthesia in patients to whom the usual dose of atropine has been given pre-operatively. The influence of this arrhythmia on the cardiac output is unknown. Its presence can only be recognized with accuracy by the direct observation of the galvanometer string of an electrocardiograph. It can be recognized sometimes by observing the synchronous pulsations of the carotids and jugulars. I have auscultated a few cases and there was a marked decrease in the intensity of the heart sounds during the periods of A-V nodal rhythm. During anaesthesia, A-V nodal rhythm can be abolished, with the return of sinus rhythm, either by decreasing the concentration of the inhaled vapours or by using a less irritant agent.

True bradycardia during anæsthesia must be carefully distinguished from an apparent bradycardia due to alternating interpolated ventricular extrasystoles which are not conducted to the peripheral arteries. This differentiation is important as the latter arrhythmia can be abolished by assisting the respiration or by adding ether whereas this procedure will aggravate a true bradycardia and may precipitate a cardiac arrest.

It is concluded that it is essential to use an electrocardiograph during anæsthesia in patients with myocardial disease or during prolonged operative procedures. It is well worth the extra trouble as, if a regular sinus rhythm is maintained throughout at between one hundred and one hundred and thirty beats a minute, the recovery of the patients from anæsthesia will be rapid and uneventful. Auricular fibrillation appears to be uninfluenced by general anæsthesia, but the tendency towards the occurrence of ventricular arrhythmias remains unaltered and these arrhythmias can be controlled in the manner already described. The dangers associated with the administration of an inhalation anæsthetic to an inadequately atropinized patient have been illustrated. This may explain the sudden deaths that have been attributed to status lymphaticus.

The influence of thiopentone on cardiac rhythm and on the cardiac arrhythmias will be discussed in a future paper.

#### SUMMARY

An electrocardiographic study has been carried out on sixty healthy subjects. It has been demonstrated that cardiac inhibition, to the point of complete cardiac arrest, may occur as the result of inhaling cyclopropane or ether. The degree of inhibition varies directly with the irritancy of the inhaled vapour.

The inhibition of the heart appears to be due to stimulation of vagal nerve endings in the air passages by the anæsthetic agent. The stimulation causes reflex inhibition of the heart through the pulmo-cardiac reflexes.

Atropine will prevent the more serious degrees of inhibition in all except the most vagotonic subjects. Doses of 1/50 of a grain or less do not prevent the occurrence of A-V nodal rhythm during anæsthesia.

The intravenous administration of atropine to anæsthetized subjects in a state of increased CO<sub>2</sub> tension may cause ventricular tachycardia. It has been suggested that the simultaneous administration of atropine and prostigmine may potentiate the sympathomimetic effect of atropine, with fatal results.

It has been advised that the muscular relaxation obtained with the initial dose of curare should be maintained by anæsthetic agents and not by the administration of more curare, in so far as abdominal surgery is concerned. This procedure eliminates the need for prostigmine.

The more frequent use of the electrocardiograph during anæsthesia has been advocated.

I wish to express my gratitude to Mr. E. S. Gawne, F.R.C.S., for granting me permission to carry out this investigation and for his co-operation during the experiments.

I should also like to thank Messrs. Tytherington Products Ltd., of Cheadle Cheshire, who are producing a combined anæsthetic apparatus and electrocardiograph in conjunction with Messrs. A. C. Cossor of London.

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